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T2* Mapping of Articular Cartilage

Current Status of Research and First Clinical Applications

Gustav Andreisek, MD, MBA and Markus Weiger, PhD†*

Abstract: T2* mapping is a relatively new method for the compositional assessment of the articular cartilage. Typically, a multigradient echo or an ultrashort echo time imaging technique with a range of short and very short echo times is used. In most studies, imaging is performed at a high field strength, that is, 3 and 7 T. Postprocessing includes exponential fitting of relaxation decay and manual region-of-interest–based measurements of T2* times on T2* maps. Detailed analyses of T2* times of articular cartilage have shown distinct T2* components with shorter and longer T2* times. Moreover, there is a zonal distribution with a significant depthwise gradient of T2*, with relatively short times near the osteochondral junction and relatively long times at the cartilage's surface. T2* times of normal articular cartilage at the knee are, when averaged over the whole cartilage thickness and using monoexponential fitting, approximately 20 milliseconds. The results of recent studies have shown a good test-retest as well as interreader and intrareader reliabilities for T2* mapping. This article provides a descriptive review of the current literature, briefly discusses the technique itself, and provides an outlook on future research questions and possible clinical applications.

Key Words: magnetic resonance imaging, articular cartilage, T2* mapping

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BACKGROUND

The articular cartilage is a highly specialized tissue and has a complex ultrastructure. It mainly consists of water (approximately 75%), collagen and proteoglycans (approximately 24%), and cellular material, that is, chondrocytes (approximately 1%). It typically shows a zonal microanatomy with collagen fibers oriented perpendicular to the surface in the deep layers and parallel to the surface at the very superficial layer. The articular cartilage has unique biomechanical properties because it distributes the load to the bone while providing a low-friction, weight-bearing surface. Overall, the articular cartilage is essential for the biomechanical function of joints.[1–3]

Articular cartilage can acutely be damaged during trauma and chronically by degenerative changes. The common pathway for both types of damage is the development of osteoarthritis. In very early osteoarthritis, there is often no obvious morphological change to the cartilage tissue. Usually, the articular cartilage is intact without superficial fissures, often one of the first morphological signs of cartilage degradation. Advancing osteoarthritis, at some point, leads to morphological changes, which include further fissuring, clefts, and loss of substance. The goal of modern quantitative imaging techniques is to detect such very early changes in the articular cartilage. Detection of changes within the articular cartilage at the absence of early morphological changes on standard imaging would be favorable in terms of preventive approaches and potential cartilage-preserving therapies.

With the event of new therapeutic options such as dietary supplementation, intra-articular injection of hyaluronic acid, reparative techniques (eg, abrasion, microfracturing, drilling), and reconstructive techniques (eg, autologous chondrocyte implantation, matrix-induced chondrocyte implantation, and osteoarticular transfer), diagnosis of early changes has become increasingly important. Follow-up imaging and monitoring of the therapeutic effects of any of those treatment options also demand for advanced reliable imaging techniques.[3]

Magnetic resonance imaging techniques for assessing the articular cartilage can be distinguished into techniques for evaluation of either its morphology or its composition. Techniques for morphologic assessment include all standard 2-dimensional (2D) magnetic resonance (MR) sequences such as spin-echo (SE) and fast SE (FSE) sequences as well all 3-dimensional (3D) sequences (3D FSE, 3D spoiled gradient echo, 3D dual echo steady state, 3D balanced steady-state free precession, 3D driven-equilibrium fourier transformation, and 3D FSE sampling perfection with application optimized contrast using different flip angle evolutions).[1,3] Strengths and drawbacks of each different morphologic imaging sequence vary and were discussed in detail in a recent publication by Crema et al.[3] In this article, various techniques for compositional articular cartilage assessment are presented, additionally including T2 mapping, delayed gadolinium enhanced magnetic resonance imaging of cartilage (dGEMRIC), T1ρ mapping, sodium imaging, and diffusion-weighted imaging.[1,3–5] However, there is another technique for evaluating the articular cartilage, which has recently gained much interest, namely, T2* map ping. A sharp increase in publications was seen lately,[2,6–15] with first clinical trials already showing the application of this technique in diseased cartilage and in patients. To the best of our knowledge, there is currently no comprehensive overview of the current status of research in T2* mapping. Thus, the purposes of this article were to provide a descriptive review the current literature, to briefly discuss the technique itself, and to provide an outlook on future research questions and possible clinical applications. A search in the MEDLINE and EMBASE databases as well as the Cochrane Library was performed using standardized key words (T2*, T2star, T2 mapping, mapping and cartilage, and MR imaging and cartilage) to identify all relevant articles.

TECHNIQUE

Similar to T2 mapping, T2* mapping uses the characteristics of transverse relaxation of the articular cartilage. It is known from several studies that the transverse relaxation of cartilage contains different components.[8,16–20] In agreement with several previous reports,[17,18,20] a recent study by Reiter et al[16] described 3 components, with the first component showing T2 times of approximately 2 milliseconds and the second and third components showing T2 times of approximately 25 milliseconds and 150 milliseconds, respectively. The authors assigned the components, with the T2 increasing, to relatively immobile collagen-bound water, to water bound to the articular cartilage's proteoglycans, and to water loosely associated with proteoglycans.[16] Another in vitro study by Lattanzio et al[21] observed 4 different components with T2 times of approximately 0.02, 1, 4, and larger than 20 milliseconds. The authors assigned those 4 components to collagen,

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From the *Department of Radiology, University Hospital Zurich; and †Institute for Biomedical Engineering, University and ETH Zurich, Zürich, Switzerland.
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Reprints: Gustav Andreisek, MD, MBA, Head MSK Imaging Research Group, Department of Radiology, University Hospital Zurich, Raemistrasse 100, CH-8091 Zurich, Switzerland. E-mail: gustav@andreisek.de.

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mobile macromolecules (ie, proteoglycans), collagen fibrillar water (ie, water trapped within collagen fibrils), and bulk water. Although the exact number and assignments of the different relaxation components is still unclear and although there are some interpretational differences among previous studies, they all agree on the existence of a long transverse relaxation component in the articular cartilage of approximately 20 to 30 milliseconds associated with bulk water and a short-living component with a T2 of 2 to 4 milliseconds, which is commonly assumed to be associated with relative immobile collagen-bound water.[16,18–21]

Local T2 values can be determined through T2 mapping using multiecho (ME) SE methods.[3] As a more time-efficient alternative, T2* mapping can be performed using ME gradient recalled echo (GRE) techniques. Studies using 2D or 3D ME-GRE techniques typically used a range of echo times (TEs) between 4 and 70 milliseconds,[6,7,12,13,15,22–24] which enabled to measure T2* times of the longer components (>20 milliseconds). However, because shorter TEs are usually not possible with clinical imaging sequences, the very short-living components cannot be detected with these techniques.

Yet, the short component with T2 of approximately 2 to 4 milliseconds would be of particular interest in the course of the aforementioned osteoarthritis development, which includes deterioration of the collagen network in the early phase. More recently, ultrashort TE (UTE) imaging is being used for T2* mapping of the articular cartilage, which allows to decrease TE to 0.5 milliseconds or even 8 μs and to detect the short components.[8,10,25–27] Very recently, Du et al[10] presented a new technique where a dual adiabatic inversion recovery UTE sequence was used to selectively visualize the short-living T2 components of the articular cartilage. It uses adiabatic preparation pulses, which invert and null the magnetization of the longer T2 components of the articular cartilage and of marrow fat of the adjacent bone.[28] In general, 2D and 3D versions of UTE imaging exist, readouts are performed on radial or spiral trajectories, and the acquisitions with different TEs are performed either after a single or after separate excitations.

Geometric parameters were different among recent studies depending on whether articular cartilage specimens were scanned in vitro[12,27] or whether patients underwent imaging.[7] In these studies, in-plane resolution ranged from 0.12 to 0.39 mm for in vitro imaging and 0.42 to 0.6 mm for in vivo imaging. The choice of radiofrequency coils depended on the subject matter and limits comparability of studies because coil-related differences in the signal-to-noise ratio of the raw images influence the fitting accuracy of the relaxation time calculation.[14,29] Most current studies were performed using a 3.0-T scanner from 1 of the 3 main vendors (Siemens Healthcare, Erlangen, Germany; GE Healthcare, Waukesha, WI; Philips Healthcare, Best, The Netherlands). Only 1 group has published data from a 1.5-T scanner,[30] and so far, only 1 group from Vienna has published data from a 7.0-T scanner (Siemens).[22,31] Acquisition time was relatively short in most studies (<5 minutes) and related to the total scan volume. Postprocessing included fitting of the relaxation decay for which algorithms typically written in MATLAB (The Mathworks Inc, Natick, MA)[11,16,30] or interface definition language (IDL; Exelis Visual Information Solutions, Boulder, CO),[31] dedicated software (MRIMapper software; Beth Israel Deaconess and MIT 2006),[26] or inline processing packages (SyngoMapIt; Siemens)[7,12] were used, as well as region-of-interest (ROI)–based measurements of T2* times on T2* maps. For the latter, manual ROI placement was used in all studies, again using various software packages.[7,11,12,14,32] In addition, fractions of the different T2* components were determined in some studies.[8,16–20,27]

POTENTIAL OF T2* MAPPING

An ex vivo study by Qian et al[27] evaluated the different components of the articular cartilage using UTE-based T2* mapping with the shortest TE approaching 0.5 milliseconds and the longest TE being 40 milliseconds with 11 steps in between. Four different types of T2* decay models with monoexponential, biexponential, triexponential, and nonexponential characteristics were used for the identification of the different transverse relaxation components. Short T2* components with a range of 1 to 6 milliseconds were found and assigned to trapped water. Components with long T2* times of approximately 22 milliseconds were also detected and assigned to free (bulk) water molecules. In addition, the triexponential decay model showed a very short T2* component of less than 2 milliseconds, which was considered to represent contribution from fragmented (mobile) proteoglycans.[27] In their study, Qian et al[27] also imaged enzymatic degraded cartilage specimen and found that, in the diseased cartilage, the short T2* times (1–6 milliseconds) were shortened. There was no effect, however, on the long T2* times (>20 milliseconds). Different findings were reported in a very recent study by Pauli et al,[8] who compared T2* mapping with biexponential analysis and T2 mapping with monoexponential analysis of human cadaveric patella cartilage with results from histopathology and optical microscopy. In this study, osteoarthritis did not significantly affect the T2* value of the short-living component, but it was rather correlated with an increase of its fraction. Furthermore, a significant reduction of the longer T2* value was observed but not of T2.[8] Bittersohl et al[14] performed 2 studies where T2* mapping of hip articular cartilage was applied to 21 femoral head specimens collected from patients with osteoarthritis who underwent total hip arthroplasty[12] and in 29 patients with femoroacetabular impingement. The authors were able to demonstrate that, with increasing severity of osteoarthritis (as assessed using the modified Outerbridge classification), T2* times in diseased portions of articular cartilage decreased.[12,14] An important observation in these studies was that the most pronounced drop of T2* was seen in the early phase of osteoarthritis, namely, between the Outerbridge grade 0 and grade 1. This is very advantageous for all future clinical applications because it indicates the potential capability of T2* mapping for detection and monitoring of early osteoarthritis. However, Bittersohl et al[9] did not perform an analysis of the different T2* components and fractions. A study by Marik et al[13] in 10 patients with osteochondral defects of the talus and 9 healthy control participants showed contradictory results with increasing T2* values in the diseased cartilage. However, this study was limited by the fact that the cartilage at the talus is very thin and the image resolution was relatively low (0.4 mm × 0.4 mm) at a slice thickness of 3 mm. As a result, the reported mean (SD) of the obtained T2* values was fairly high at the overall small T2* differences between patients with moderate cartilage disease and healthy control participants (11.8 [2.7] milliseconds vs 16.1 [3.2] milliseconds, respectively).[13]

Overall, T2* mapping has the potential to quantitatively reflect loss of collagen fiber integrity and changes in bound water, which are the typical early findings in the development of osteoarthritis.[6,22,27]

REPRODUCIBILITY

Similar to every new imaging technique, T2* mapping has to prove its reproducibility as well as interobserver and intraobserver reliabilities. Whereas evidence in the literature for the other compositional imaging techniques is rather good,[1] there are only a few studies presenting reproducibility data of T2* mapping.[11,25,26] Williams et al[25] imaged the knees of 11 healthy participants on 3 consecutive days always during the same hours of the day. The authors observed a precision error of 8% that corresponds to a mean (SD) T2* time error of 1.2 (1.0) milliseconds when they measured the overall T2* times of the femoral and tibial articular cartilage within the central weight-bearing zone of the medial femorotibial compartment. Newbould et al[11] performed a similar study and evaluated the test and retest variability by imaging the knees of 18 healthy participants twice a day during a single visit. The authors reported a lower error with a 2.0% within-subject coefficient of variation across the entire knee cartilage. However, detailed data showed that the coefficient of variation was much greater (up to 7.7%) when only portions of the knee cartilage were analyzed. It needs to be noted that neither study looked at the different T2* components but rather focused on the overall T2* time of cartilage. One of the conclusions that might be drawn from these 2 studies is that the thinner the cartilage, the greater usually the observed variability.[11,25] This might be related to operator-dependent differences in the segmentation of small structures and could be improved in the future using automated segmentation software.

In the study by Williams et al,[25] the authors evaluated the intraobserver variability. Therefore, 1 reader repeated all ROI-based measurements after 3 months. Intraclass correlation coefficients were calculated and ranged between 0.80 and 0.98, which corresponds to an excellent intraobserver agreement using the interpretation of Landis and Koch.[33] This interpretation was also supported by the fact that no significant differences could be detected between the first and second ROI-based measurements by Williams et al.[25] Another study by Bittersohl et al[14] also reported intraobserver data. In this study, where 21 femoral head specimens were imaged, 1 reader performed repeated measurements with a 4-week delay in a small proportion of the specimens (n = 10). The intraclass correlation (ICC) was found to be 0.949.

Robust data for the interobserver agreement of T2* measurements were published by Welsch et al.[22] In this study, 3 authors with very different levels of experience (a senior musculoskeletal radiologist with 25 years' experience, an orthopedic surgeon with 10 years' experience, and a young radiologist with 2 years' experience) performed ROI-based segmentations on T2* maps. As usual in such a study setting, ICCs were calculated. They turned out to be, on average, 0.903 for T2* mapping at 3.0 T. The study by Welsch et al[22] is, to the best of our knowledge, so far the only study that, in addition, reported reproducibility data for T2* mapping at 7.0 T. Interobserver variability at 7.0 T was slightly higher with ICCs, on average, being 0.875. This somewhat lower interobserver agreement at 7.0 T was most likely related to the enhanced susceptibility artifacts near the cartilage-bone interface at 7.0 T, which may obscure the true cartilage

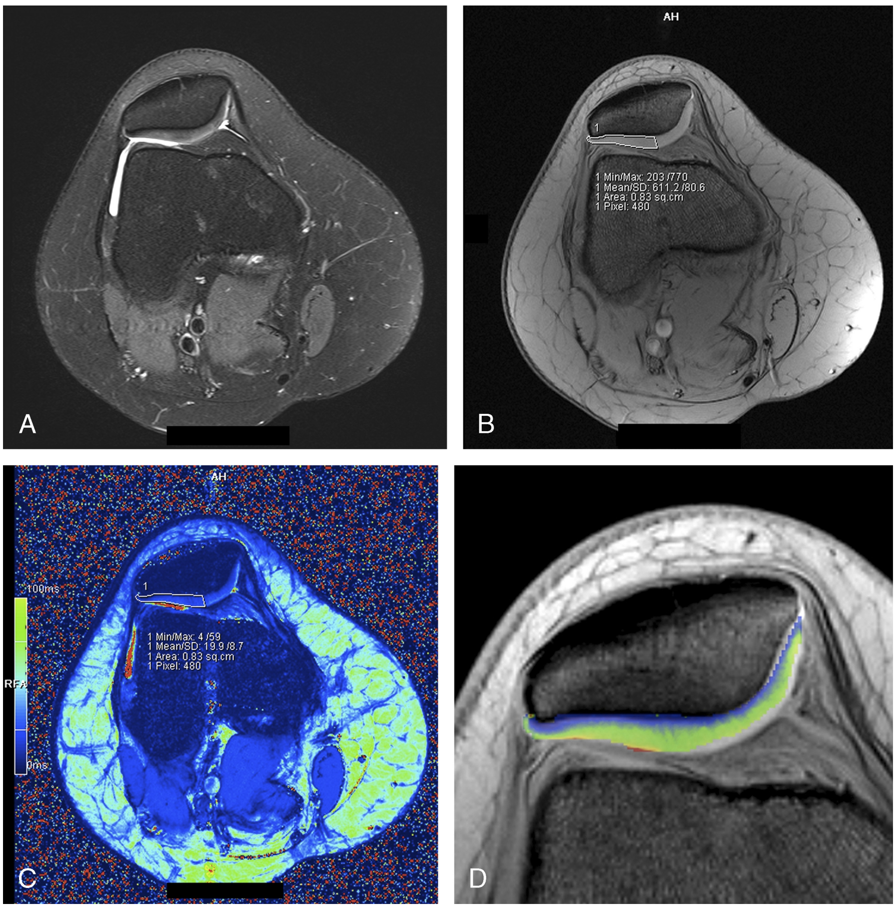

FIGURE 1. A to D, Magnetic resonance images of the right knee of a 37-year-old male healthy volunteer acquired at 3.0 T. A, Standard transaxial intermediate-weighted FSE MR image (repetition time [TR]/TE, 2640/41 milliseconds; turbo factor, 7) shows normal morphology of the retropatellar cartilage without any superficial lesions. B, Corresponding single-echo (TE, 4.4 milliseconds) MR image from a multiecho 2D fast low-angle shot (FLASH) GRE MR sequence (TR, 620 milliseconds; TEs, 4.4, 11.9, 19.4, 27.0, 34.5 milliseconds; in-plane resolution, 0.4 mm). C, Corresponding T2* map calculated with monoexponential fitting illustrates how ROI-based measurements of the T2* times of the lateral aspect of the patellar cartilage are typically performed. Please note the scale for the color-encoding of the T2* map on the left image margin. D, Magnified overlay image shows depthwise distribution of normal T2* times.

borders and have possibly hampered manual ROI placement by the observers. In general, interobserver agreement was better for the superficial portions of articular cartilage, most likely because of the better outline of the cartilage surface with respect to the surrounding joint fluid.

ZONAL DISTRIBUTION

Corresponding to previous descriptions of a distinct zonal distribution of T2 across the whole articular cartilage substance,[34,35] T2* also exhibits a clear zonal distribution with typically very low T2* times in the area of the calcified zone near the bone-cartilage interface and higher T2* times at the cartilage surface (Fig. 1).[10] Williams et al[25] used a UTE sequence with a minimal TE of 0.5 milliseconds and demonstrated an almost-linear increase in monoexponentially fitted T2* from the deep to the superficial portions of articular cartilage (Fig. 3 in the study of Williams et al[25]). The results of the statistical analysis of this depthwise variation of T2* showed that the lowest T2* occurring next to the subchondral bone was significantly different from T2* times toward the articular surface ($P < 0.001$). Zonal variation is seen for all field strengths used, that is, 3.0 and 7.0 T.[25,26] As expected, T2* times at 7.0 T were somewhat lower compared with 3.0 T. Mean (SD) T2* values for the patellar cartilage were 27.6 (4.3) milliseconds at 3.0 T and 18.3 (4.9) milliseconds at 7.0 T, respectively.

The zonal behavior was generally confirmed by the study of Pauli et al,[8] but different T2* values were obtained after bi-exponential fitting. They also showed an increase of the fraction of the short-T2* component from the superficial to the deep zone, an observation that may explain the stronger decrease of T2* reported in the study of Williams et al.[25]

TECHNICAL CONSIDERATIONS AND LIMITATIONS

A major advantage of T2* mapping versus T2 mapping is the ability of the used UTE techniques to detect signal with much more rapid transverse relaxation, down to the order of 1 millisecond or even lower (Fig. 2). Considering the zonal distribution, this enables to gain detailed information from cartilage areas even near the subchondral bone, the so-called zone of calcified cartilage, as very

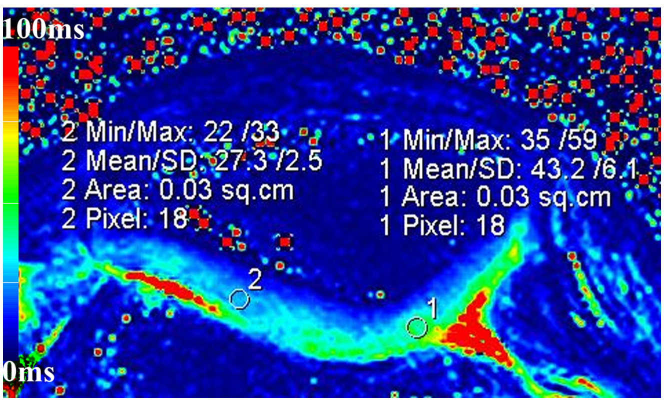

FIGURE 2. Magnified T2* map of the retropatellar cartilage of the right knee in a 45-year-old female patient, which was calculated from a multiecho 2D FLASH GRE MR sequence (3.0 T; TR, 625 milliseconds; TEs, 4.4, 11.9, 19.4, 27.0, 34.5 milliseconds; in-plane resolution, 0.4 mm). Full thickness of the retropatellar cartilage was preserved without signs of focal loss; however, in the central portion, areas with increased T2* values (ROI position 1) are seen within the cartilage with an otherwise normal zonal behavior (ROI position 2).

recently shown by Du et al,[8,10,26] who reported T2* values from 1.0 to 3.3 milliseconds for the ZCC. In contrast to T2, T2* also reflects signal decay associated with local field gradients. T2* alterations due to macroscopic field gradients related to tissue interfaces and imperfect shimming must be considered as artifacts (Fig. 3). As mentioned by Mamisch et al,[7] this could be a particular issue in the daily clinical setting where patients with metallic implants are imaged or when metallic particles are present as a result of a prior surgery.[7] However, T2* changes due to microscopic field gradients reflecting structural properties of the tissue can contain valuable information that is not present in T2 data. Note that, depending on the field distribution across the image voxel, the observed signal decay is usually not purely exponential, which can degrade the results of the fitting procedure. To solve this problem, more advanced fitting would be required, incorporating appropriate modeling of the signal evolution.

Another important factor and limitation affecting measurements of transverse relaxation is the magic angle effect, which has been described in numerous publications.[27,30,36–40] Shiomi et al[30] specifically investigated T2* mapping of the articular cartilage and demonstrated statistically significant changes in T2* depending on the angulation of a joint with respect to the main magnet field. However, Pauli et al[8] found that T2* values are less affected by orientation than T2 values are and that the fractions of the components do not change significantly. Generally, it should be taken into account that the magic angle effect may severely influence the comparability of longitudinal studies when identical subject positioning is not always guaranteed over time.

Specific technical challenges are posed by the UTE techniques, targeting extremely short TEs. The initial gradient ramping used during acquisition makes the sequences particularly susceptible to both off-resonance– and eddy current-related artifacts, thus requiring careful implementation and setup.[28]

FURTHER RESEARCH AND POTENTIAL CLINICAL APPLICATIONS

Currently, only few studies that describe the first clinical applications of T2* mapping in human articular cartilage exist. Bittersohl et al[41] determined the normative T2* values of the articular cartilage of the glenohumeral joint in 40 healthy participants using a 3D ME data image combination sequence with 6 echoes with a minimum TE of 6.9 milliseconds. The same authors evaluated, as mentioned previously, T2* times of hip cartilage in 29 patients with femoroacetabular impingement using a similar technique.[14] Buchbender et al[15] used T2* mapping, along with native T1 mapping, dGEMRIC, and ΔR1 imaging to assess articular cartilage changes of the metacarpophalangeal joint in 16 patients with rheumatoid arthritis compared with 13 healthy control participants. The previously mentioned study by Mamisch et al[7] performed T2* mapping in patients who underwent a microfracturing procedure in the weight-bearing areas of the femoral knee cartilage. Although an ME-GRE sequence that had a minimum TE of only 5.7 milliseconds was used, the distinct zonal (depthwise) distribution of T2* could be demonstrated in both a healthy control group and the patients who all had microfracturing. Means (SDs) of T2* times in the fibrocartilaginous repair tissue were between 21.0 (4.8) milliseconds (deep zones) and 27.7 (3.4) milliseconds (superficial zones). To the best of our knowledge, the study by Mamisch et al[7] is the first to describe T2* mapping in postoperative patients.

Future research should focus on standardization of pulse sequences, imaging parameters and protocols, as well as postprocessing techniques including the different (multiexponential) exponential fittings. Appropriate fitting models have a tremendous impact on the detection of the exact number of transverse relaxation components and their assignments to pathological changes in the biochemical

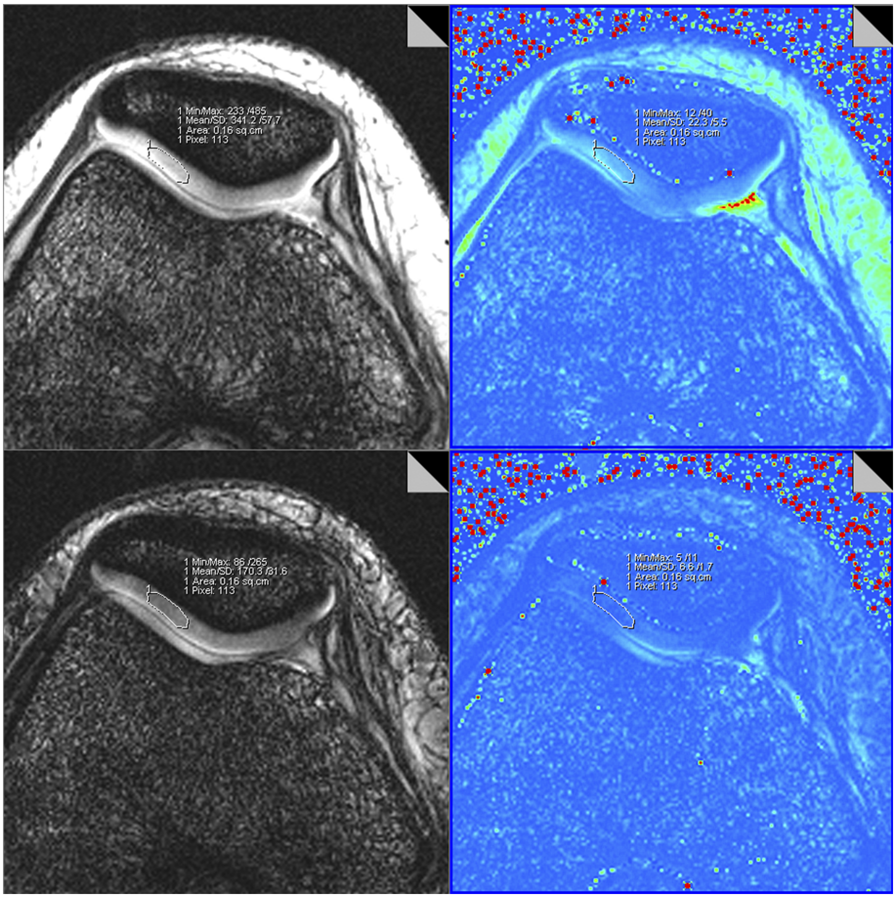

FIGURE 3. Set of MR images of the right knee of a 25-year-old female healthy volunteer to simulate inappropriate shimming. A multiecho 2D FLASH GRE MR sequence (3.0 T; TR, 364 milliseconds; TEs, 4.4, 11.9, 19.4, 27.0, 34.5 milliseconds; in-plane resolution, 0.4 mm) was used. Left, Gray scale images acquired at a TE of 19.4 milliseconds. Right, The corresponding T2* maps are shown. The window-and-level setting of the gray scale images as well as the color coding of T2* maps were kept identical. The upper and lower images only differ in the field homogeneity, which was automatically optimized by the scanner (upper images) and voluntarily mis-set along the Z dimension (lower images) by the operator by applying a linear magnetic field gradient of 200 μT/m. Free-hand ROIs were drawn on the anatomic images and copied to an identical location on all 4 images. Mean (SD) T2* time was 22.3 (5.5) milliseconds (upper-right image) and 6.6 (1.7) milliseconds (lower-right image), illustrating a false T2* relaxation time calculation in case of inappropriate shimming.

composition of the articular cartilage. Similarly, the selection of TE times and the signal-to-noise ratio of the acquisition significantly influences the ability of T2* mapping to detect early changes in the tissue. The influence of magic angle effects requires further investigation, as does the influence of motion in between the single-echo acquisitions. Misregistration is likely to have a significant effect on T2* reliability because it has been seen in recent dGEMRIC studies in a similar way.[23,42,43] Finally, selection of ROIs would benefit from more user-independent, automated tools. Ultimate acceptance of T2* mapping as a clinical method might be reached by future studies by tracking biochemical or ultrastructural changes of the articular cartilage in early osteoarthritis. Currently, however, there is no sufficient evidence to recommend this technique for the clinical routine. It will be the task of future clinical studies to determine which one of the various compositional imaging methods (eg, T2, T2*, dGEMRIC, T1ρ mapping, sodium imaging, and diffusion-weighted imaging) is the best predictor for earliest osteoarthritis and should therefore be added to clinical imaging protocols. Our hypothesis, however, is that a combination of 2 or more methods will finally be needed because they focus on different aspects/biochemical structures of the cartilage and provide complementary information.

SUMMARY

T2* is a relatively new quantitative biomarker for the articular cartilage. T2* maps are produced from MR imaging data obtained with ME-GRE and UTE sequences using exponential fitting methods. Local T2* values are determined using manual ROI-based measurements. The results of preliminary studies show a good test-retest as well as interreader and intrareader reliabilities. Unfortunately, only a few clinical studies are currently available, which severely limits the data on hand in the literature and leaves many research questions unanswered. However, T2* mapping has a great potential for noninvasive compositional cartilage assessment with several inherent advantages over the widely used quantitative cartilage imaging techniques such as T2 mapping. Currently, T2* mapping needs to be considered as a very interesting research method

with high potential and future clinical studies with histopathological correlation are strongly recommended.

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